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A MEDICAL LETTER STATEMENT ON SMOKING AND LUNG CANCER

Dr. John H. Talbott, Editor of the AMA Journal, has advised physicians (JAMA, Dec. 12, 1959) to wait for "definitive studies" before making up their minds about the causal connection between smoking and lung cancer. In the opinion of Medical Letter consultants, physicians should not wait for more studies before warning patients that smoking does increase the risk of lung cancer.

Dr. Talbott's signed editorial in the Journal questions the validity of a statement by Dr. Leroy E. Burney, Surgeon General of the Public Health Service, which appeared in the Journal two weeks earlier. Dr. Burney, after reviewing the evidence, concluded that smoking is "the principal etiological factor in the increased incidence of lung cancer." But according to Dr. Talbott, "a number of authorities who have examined the same evidence cited by Dr. Burney do not agree with his conclusions." If physicians were to demand unanimous agreement among authorities for medical or public health decisions, they would rarely make a diagnosis, prescribe a drug, or undertake a public health project.

The preponderance of evidence incriminating smoking has been such as to convince eminent epidemiologists, pathologists, clinicians and cancer investigators, as well as the American Cancer Society, the National Cancer Institute, the American Public Health Association, the British Ministry of Health, the British Medical Research Council, and the State Medical Research Council of Sweden. In fact, the probability of a connection between smoking and lung cancer is now so great that for practical purposes in advising his patients, the practicing physician would do well to regard it as proved.

THE REFUTATION - Dr. Burney's report provides statistical, pathological, chemical and experimental evidence to support his conclusions. In questioning these conclusions, Dr. Talbott states that the studies on smoking and lung cancer "do not explain why, even when smoking patterns are the same, case rates are higher among men than among women, and among urban than among rural populations." But as Dr. Burney points out, there may be a "true sex difference in susceptibility...to lung cancer."

There is no reason why a sex difference should be more remarkable in the mortality rate for lung cancer than, for example, stomach cancer (which is far more frequent in men than in women), or for pulmonary tuberculosis. The con-

siderably higher mortality rate for pulmonary tuberculosis in females than in males does not negate the significance of the tubercle bacillus in the etiology of pulmonary tuberculosis. Aside from specific sex differences in susceptibility, a part of the disparity between male and female lung cancer mortality can probably be accounted for by the fact that on the average, men have been smoking for longer periods than women (W. Haenszel, et al., Public Health Monograph, No. 45, 1956).

As for differences between rural and urban areas, "the lung cancer death rate was found to be somewhat higher in cities than in rural areas.... In all areas, the lung cancer death rate was very low among men who never smoked regularly and high among regular cigarette smokers." (E. C. Hammond, Amer. Scientist, 46:331, 1958). This finding simply supports the hypothesis that air pollution is another important cause of lung cancer.

Dr. Talbott urges that until "definitive studies are forthcoming" the physician should watch the situation closely and advise his patients on the basis of his own appraisal of the facts. Aside from the difficulty a busy practitioner has in keeping sufficiently informed of the facts to make a scientific judgment, the question arises as to what is a "definitive study." And how much additional evidence is necessary to incriminate smoking as a cause of lung cancer before personal and public health measures are to be advocated? In 1849, Dr. John Snow showed a connection between cholera and the drinking of polluted water. Thirty-four years later Koch demonstrated the presence of the cholera vibrio as the responsible organism. Should steps to eliminate water pollution have waited for Koch's demonstration? Obviously not, and the parallel with cigarette-smoking seems clear.

There are many gaps in our knowledge of the etiology and pathogenesis of lung cancer. But highly convincing studies are at hand to support the conclusion of Dr. Burney and others that smoking, particularly of cigarettes, is an important etiologic factor in the increased incidence of lung cancer; that "stopping cigarette smoking even after long exposure is beneficial"; and that "the nonsmoker has a lower incidence of lung cancer than the smoker in all controlled studies, whether analyzed in terms of rural areas, urban regions, industrial occupations, or sex." (L. E. Burney, JAMA, 171:1829, Nov. 28, 1959).

IMFERON

When iron-deficiency anemia must be treated parenterally, iron-dextran (Imferon-Lakeside) offers the great advantage of intramuscular administration and thus eliminates serious hazards encountered with earlier intravenous preparations. Whether Imferon introduces other hazards is still to be determined. In a recent study (H. G. Richmond, Brit. Med. J., 1:947, 1959), sarcomas were induced in rats by the injection of massive doses of iron-dextran. Because of the dosage, and because rats are particularly susceptible to sarcoma induction, the significance of this study is questionable. Nevertheless, the great variation in susceptibility among humans means that the possibility of sarcoma induction cannot be completely ruled out. Despite this unconfirmed possibility, Imferon is probably less hazardous than other parenteral iron preparations; but it should

not be used unless iron deficiency has been clearly established, and then only in patients with whom it is impossible to use oral iron therapy effectively.

Another reason for caution in parenteral therapy arises from the unique metabolism of iron in the body. Very little iron is excreted by normal subjects; hence, with parenteral preparations containing 50 mg. of elemental iron per cc. (as in Imferon) it would take only about 90 cc. to double the normal total body content of iron. Before starting parenteral therapy, therefore, the physician should be certain that he is dealing with depleted iron reserves and not excess stores of iron - a determination that is not always simple. For example, patients with thalassemia characteristically have a morphologic type of anemia (microcytic and hypochromic) similar to that observed in patients with iron deficiency. Yet in this condition the tissue stores of iron are greatly in excess of normal, and giving more iron enhances the development of hemosiderosis.

INDICATIONS FOR PARENTERAL THERAPY - Iron therapy is of value in the treatment of iron-deficiency anemia and in no other condition. Furthermore, the great majority of patients with iron deficiency can be treated safely and inexpensively with soluble ferrous iron salts given orally (The Medical Letter, July 24, 1959). The only indications for parenteral administration are:

1. Intolerance to oral iron. This is considered a valid indication only after oral therapy has been given a proper trial. Fast response is rarely vital. Most patients will tolerate oral iron therapy if the iron is given with meals, and if the dose is begun at low levels and gradually increased.
2. Impaired gastrointestinal absorption of iron. This occurs in some patients with steatorrhea or resections of portions of the gastrointestinal tract.
3. Need for rapid restoration of hemoglobin levels. This group is a very small one. In a woman with severe hypochromic anemia who is seen for the first time in the last trimester of pregnancy, there may be justification for parenteral iron therapy. There is no justification for the routine use of parenteral iron in pregnant women.

SIDE EFFECTS - Such reactions to intramuscular injections of Imferon as nausea, vomiting, fever, chills, headache, arthralgia, urticaria, and asthma have been observed in some patients. Toxic reactions and side effects have been neither as frequent nor as serious as with intravenous iron preparations, which have occasionally caused syncope, shock, convulsions and death.

DOSAGE - For adults, a maximum of 5 cc. of solution may be given in a single injection into each buttock, and therapy may be repeated daily until the required amount of iron has been given. Directions, cautions and appropriate dosage charts based on body weight and hemoglobin levels accompany the Imferon package.

Unless there is an increase in hemoglobin concentration of at least 2 Gm. per 100 cc., or an increase in the volume of packed red cells of at least 5 cc. per 100 cc. in three weeks, iron should be discontinued and the following possibilities considered: (1) the anemia is not due to iron deficiency; (2) complicating disease impairs the ability of the marrow to respond; or (3) there is continued active blood loss.

POVAN AND OTHER ANTHELMINTIC DRUGS

Infections by the nematode Enterobius vermicularis (pinworm) probably receive more treatment in this country than do those from all other intestinal parasites combined, and the marketing of a new drug which promises to be safe and effective in a single dose is welcome news. The new drug, pyrvinium pamoate (Povan Suspension-Parke, Davis), is a cyanine dye which turns the stools red. It is given in one dose of 5 cc. per 22 pounds of body weight. J. W. Beck, et al. (Am. J. Trop. Med., 8: 349, 1959) report that single-dose treatment of 100 children eliminated the pinworm in 96 without evidence of toxicity.

Until these results are confirmed, however, piperazine (Antepar-Burroughs, Wellcome, and other brands), which has been in use in various forms for some years, remains the drug of choice. It is both effective and relatively non-toxic. One daily dose (children, 250 mg. per 15 pounds; over 60 pounds, 2 Gm.) for seven consecutive days yields 95 to 100 per cent cures. With any drug, pinworm reinfection must be prevented by sanitary measures, and often, group treatment.

ROUNDWORMS AND OTHER WORMS - Piperazine is also the drug of choice in Ascaris lumbricoides (roundworm) infections, with a cure rate close to 100 per cent. The dosage for roundworm - once daily for two days - is 1 Gm. per 30 pounds or less; 2 Gm. per 30-50 pounds; 3 Gm. per 50-100 pounds; 3.5 Gm. per 100 pounds or more. If necessary the treatment may be repeated in one week.

For Trichuris trichiura (whipworm), dithiazanine (Delvex-Lilly), a cyanine dye which turns the stools blue, is the only effective treatment now available. It is also effective against pinworm, roundworm, Strongyloides, and ancylostomiasis (hookworm) infections (J. C. Schwartzwelder, et al., JAMA, 165: 2063, 1957; F. J. Aguilar, Am. J. Trop. Med., 8: 305, 1959). Dithiazanine has been reported to cause vomiting in 10 to 25 per cent of patients. The vomiting is usually mild and brief, but it may be severe. Diarrhea occurs occasionally. The dosage for adults and for children over 60 pounds is 100 mg. three times the first day and 200 mg. three times a day for four additional days. For children under 60 pounds, the average dose is one-sixth the adult dosage for every 10 pounds of body weight. For unusually resistant infections, treatment may be prolonged, but for no more than 21 days. If elimination of the parasite is not complete, a second course at the same daily dosage level and for the same period may be repeated after one to two weeks.

HOOKWORM - Dithiazanine has some effect against hookworm, but oral tetrachlorethylene in a single dose is much more effective and remains the treatment of choice. The dose of tetrachlorethylene for children is about 2 cc.; for adults, up to 4 cc. Treatment should not be followed by purgation, which has been shown to increase toxicity and to decrease effectiveness. Since the drug may produce severe dizziness or headache, it is advisable to have the patient rest for an hour or two after treatment. A single treatment completely eliminates the parasite in about 80 per cent of patients harboring Necator americanus and about 25 per cent of those harboring the much less frequent Ancylostoma duodenale. Treatment with tetrachlorethylene can be repeated every four or five days until no eggs are present in the stool.

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